Update of Intravenous Thrombolytic Therapy in Acute Ischemic Stroke

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Abstract

Upon acute ischemic stroke, rapid recanalization of the occluded cerebral vessel via intravenous thrombolytic therapy (IVT) is crucial to achieve good functional outcome. The time window of IVT with recombinant tissue plasminogen activator (rt-PA) has been extended from post-stroke 3 to 4.5 hours. In patients with cerebral penumbra identified using cerebral perfusion imaging, IVT is still beneficial within 4.5 to 9 hours after onset of stroke. For those without clear stroke onset time, DWI-FLAIR mismatch by brain MRI indicates hyperacute infarct and IVT is indicative. For patients with large cerebral vessel occlusion, endovascular thrombectomy (EVT) alone is likely non-inferior to bridging therapy (IVT followed by EVT) and this issue is still under investigation. Serial studies have provided the evidence of safety and risk of IVT in specific groups of patients, such as elderly, anticoagulant users, and those having cerebral microbleeds or seizure. Tenecteplase has higher fibrin selectivity than rt-PA and large clinical trials have demonstrated its great potential for stroke therapy. Future clinical trials are mandatory for therapeutic optimization of IVT, especially in bridging therapy, specific groups of patients, and new thrombolytic agents.

Keywords: Acute Ischemic Stroke, Cerebral Infarction, Recombinant Tissue Plasminogen Activator, Tenecteplase, Thrombolytic Therapy.

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INTRODUCTION

For acute ischemic stroke (AIS), rapid recanalization of the occluded cerebral vessel is crucial to achieve good functional outcome[1]. The benefits of intravenous thrombolytic therapy (IVT) with recombinant tissue plasminogen activator (rt-PA) in hyperacute stroke has been established for more than 25 years[2]. In Taiwan, rt-PA has been applied to AIS treatment since 2002 and the national multi-center Stroke Breakthrough Series in 2010 further improved the guideline adherence in IVT[3]. Since 2015, endovascular thrombectomy (EVT) has been prove to be another powerful treatment for AIS patients with large cerebral vessel occlusion[4]. The likelihoods of good outcome for IVT and EVT are 1.3-2.1 and 2.7-5.0, respectively[1], and both treatments have become regular

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Table 1. Breakthrough clinical trials of thrombolytic therapy in acute ischemic stroke

Trials	Design	Comparison	Patient Number	**Results**
NINDS	Multi-center double-blinded RCT	Intravenous rt-PA *vs* placebo in patients within 3 hr stroke window	312 *vs* 312	rt-PA treatment shows more favorable outcome (39 *vs* 26%, p=0.019), more sICH (6.4 *vs* 0.6%, p<0.001) and similar mortality than placebo.
ECASS III	Multi-center double-blinded RCT	Intravenous rt-PA *vs* placebo in patients within 3-4.5 hr stroke window	418 *vs* 403	rt-PA treatment shows more favorable outcome (52 *vs* 45%, p=0.04), more sICH (2.4 *vs* 0.8%, p=0.008) and similar mortality than placebo.
EXTEND	Multi-center double-blinded RCT	Intravenous rt-PA *vs* placebo in patients within 4.5-9 hr stroke window having cerebral penumbra noted by perfusion imaging	113 *vs* 112	rt-PA treatment shows more favorable outcome than placebo (35.4 *vs* 29.5%, p=0.04) with similar risk of sICH and mortality.
WAKE-UP	Multi-center double-blinded RCT	Intravenous rt-PA *vs* placebo in patients having DWI-FLAIR mismatch by brain MRI	254 *vs* 249	rt-PA treatment shows more favorable outcome than placebo (53 *vs* 42%, p=0.02) with similar risk of sICH and mortality.
DIRECT MT	Multi-center double-blinded RCT	EVT alone *vs* bridging therapy in patients within 4.5 hr stroke window	327 *vs* 329	EVT alone shows noninferiority to bridging therapy in functional outcome (OR, 1.07; 95% CI, 0.81 to 1.40) with similar risks of sICH and mortality.
EXTEND IA-TNK	Multi-center double-blinded RCT	Intravenous tenecteplase *vs* rt-PA in patients within 4.5 hr stroke window both followed by EVT	101 *vs* 101	Tenecteplase treatment shows higher incidence of reperfusion (22 *vs* 10%, p=0.002), better functional outcome and similar sICH than rt-PA.

CI indicates confidence interval; DWI, diffusion weighted imaging; EVT, endovascular thrombectomy; FLAIR, fluid-attenuated inversion recovery; hr, hour; OR, odds ratio; RCT, randomized placebo control trial; rt-PA, recombinant tissue plasminogen activator; sICH, symptomatic intracranial hemorrhage.

management in AIS in Taiwan.

In the field of acute myocardial infarction, thrombolysis with rt-PA is nearly replaced by angioplasty and stenting for coronary reperfusion, primarily because of the later one showing better myocardial salvage and clinical outcome[5]. However, the evolution of coronary reperfusion therapy may less likely occur in the stroke field in the future. Although EVT alone is able to recanalize the large- and medium-sized cerebral occluded vessels, it is extremely difficult to approach cerebral small arteries using EVT, such as for lenticulostriate and anterior choroidal arteries, etc. Notably, unlike myocardial infarction, even lacunar infarct can lead to severe function disability and should be treated aggressively[6]. Therefore, research focusing on optimization of IVT for AIS is still mandatory. Recent studies of IVT mainly aimed at the extension of therapeutic indication, risk and benefits in specific stroke patients, and new thrombolytic agents for AIS. Figure 1 summarizes the evolution of IVT trials with rt-PA, tenecteplase (TNK) and in bridging therapy for AIS. Table 1 lists some breakthrough clinical trials of IVT in AIS. This article will review the current progress in acute stroke thrombolysis while general management for IVT can refer to updated practical guidelines[7,8].

Time Window for Thrombolytic Therapy

<4.5 hours window

In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study first demonstrated the benefits and acceptable risk of IVT in

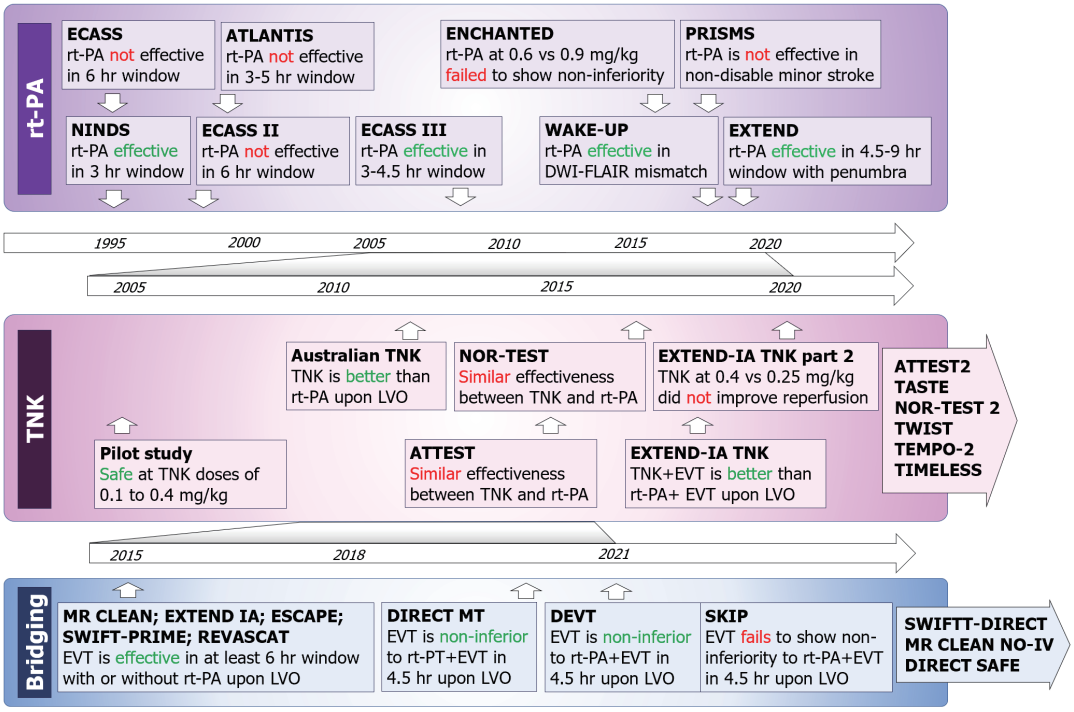

Fig. 1. Evolution of intravenous thrombolytic trials with rt-PA, tenecteplase and in bridging therapy for acute ischemic stroke. Arrow, year of publication. DWI indicates diffusion weighted imaging; EVT, endovascular thrombectomy; FLAIR, fluid-attenuated inversion recovery; LVO, large vessel occlusion; rt-PA, recombinant tissue plasminogen activator; TNK, tenecteplase.

AIS within time window of 3 hours[2]. As compared to placebo group, rt-PA treatment at 0.9 mg/kg (10% bolus followed by 90% infusion for 60 min) showed more favorable outcome (39% vs 26%, p=0.019) at post-stroke 3 months. Despite an increased incidence of symptomatic intracranial hemorrhage (sICH) (6.4% vs 0.6%, p<0.001), there was no significant difference in mortality.

It was not until 2008 that the European Cooperative Acute Stroke Study (ECASS) III trial further confirmed the usefulness of IVT in post-stroke time window of 3 to 4.5 hours[9]. Treatment with rt-PA was again associated with more favorable outcome (52% vs 45%, p=0.04), higher risk of sICH (2.4% vs 0.8%, p=0.008), but similar risk of mortality than placebo group at 3 months post-stroke. A retrospective multicenter study, which enrolled 748 Taiwanese patients supported the effectiveness and tolerability of rt-PA treatment within 3 to 4.5 hours after stroke onset[10]. Regular 0.9 mg/kg of rt-PA remains the standard dose for IVT while reduced dose at 0.6 mg/kg failed to show the noninferiority to standard-dose with respect to disability and death at 3 months[11]. In addition, the earlier treatment, the better functional outcome[12].

4.5-9 hours window

To extend the therapeutic window of thrombolytic therapy, the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) at the first time used perfusion imaging to select patients within 3 to 6 hours post-stroke who had a mismatch between perfusion-weighted MRI (PWI) and diffusion-weighted MRI (DWI)[13]. The study demonstrated that IVT was associated with significantly increased reperfusion in AIS patients having mismatch, which indicated existence of cerebral penumbra. The EXtending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial further used CT perfusion (CTP) to identify hypoperfused but salvageable regions of brain detected on automated perfusion imaging[14]. The patients were randomly assigned to receive intravenous rt-PA (n=113) or placebo (n=112) between 4.5 and 9 hours after the onset of stroke or on awakening with stroke (if within

9 hours from the midpoint of sleep). The study showed that rt-PA treatment increased the percentage of patients having favorable outcome (35.4% vs 29.5%, p=0.04) at 3 months post-stroke without significantly increased risk of sICH or mortality.

Another study, ECASS-4 trial, using MRI-based patient selection for patients within 4.5 to 9 hours post-stroke revealed non-significant trend toward better outcome in rt-PA than placebo groups (35.0% vs 28.6%, p=0.49), possibly because of relatively smaller sampled size (total n=119) than EXTEND trial[15]. The meta-analysis study combined the above three trials confirmed the overall net benefit of IVT for AIS patients 4.5-9 hours from stroke onset with salvageable brain tissue noted by cerebral perfusion imaging[16]. (Figure 2)

Unknown time of onset

Previous studies have demonstrated that a visible ischemic lesion on DWI but absence of a hyperintense signal in the same region on fluid-attenuated inversion recovery (FLAIR) of MRI is predictive of symptom onset within 4.5 hours in AIS patients[17]. The finding thus supports to the use of DWI-FLAIR mismatch for choosing IVT in AIS patients with unknown time of symptom onset. The WAKE-UP trial enrolled the patients who had an unknown time of stroke onset with DWI-FLAIR mismatch[18]. As compared to the placebo group (n=249), intravenous rt-PA treatment (0.9 mg/kg; n=254) showed more patients with favorable outcome (53.3% vs 41.8%, p=0.02) while the risk of sICH and mortality were similar between groups at post-stroke 90 days.

The Thrombolysis for Acute Wake-Up and Unclear Onset Strokes (THAWS) trial conducted in Japan tested the rt-PA dose of 0.6 mg/kg in patients with both wake-up stroke and DWI-FLAIR mismatch; there was no significant difference in percentage of patients having favorable outcome, sICH or mortality between rt-PA and placebo groups 90 days after stroke onset[19]. Nevertheless, the post-hoc analysis of the THAWS trial demonstrated

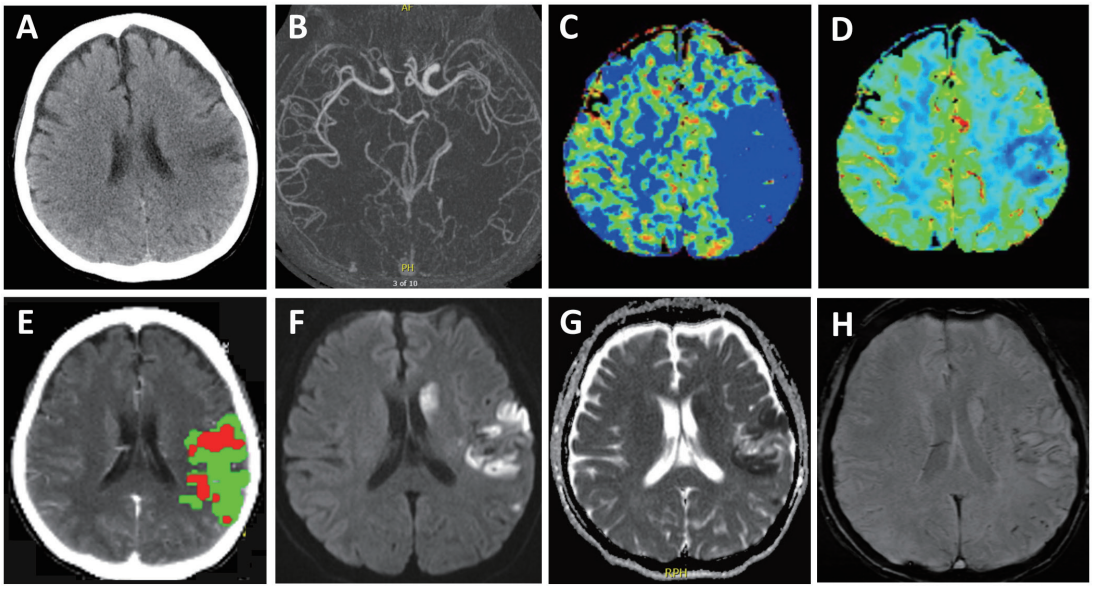

Fig. 2. A 67-year-old woman with atrial fibrillation and receiving dabigatran developed acute onset of right hemiparesis and motor aphasia (NIHSS=16). Non-contrast brain CT at 6.3 hours after stroke onset showed a small hypodensity area at the left posterior frontal region (A). CT angiography revealed branch occlusion of the left middle cerebral artery (MCA, M2) (B). Despite large cerebral hypoperfusion in the territory of the left MCA noted by mean transient time of CT perfusion imaging (C), there was only small area with reduction of cerebral blood volume (D). Automatic perfusion analysis demonstrated the areas of infarct core (red) and hypoperfusion (green) of 25 ml and 53 ml, respectively (E). The patient then received idarucizumab to reverse the effect of dabigatran, followed by intravenous thrombolysis with rt-PA. Brain MRI on the second day showed some residual infarcts in the left MCA territory by DWI (F) and ADC (G) with minimal petechial hemorrhage by SWI (H). The NIHSS improved to be 9 and she was able to walk home 2 months later.

that favorable outcome was more common in the rt-PA group in patients with DWI-ASPECTS 5 to 8 (relative risk [RR], 4.75; 95% confidence interval [CI], 1.33-30.2), but not in patients with DWI-ASPECTS 9 to 10[20]. The meta-analysis (n=843) showed that IVT resulted in better functional outcome at 90 days than placebo in patients who had a stroke with unknown time of onset with a DWI-FLAIR or perfusion mismatch[21].

Bridging Therapy

Clinical trials of endovascular thrombectomy

Five individual trials published in 2015 established that EVT significantly reduces disability rates after AIS caused by proximal occlusion of large vessels in the anterior circulation[4,22]. In one meta-analysis, the proportion of patients with a favorable outcome at 90 days was higher in the EVT (n=634) than control (n=653) groups (46.0% vs 26.5%, p<0.0001) with overall successful revascularization rate of 71% by EVT[22]. Notably, among above trials, patients in both EVT or control arms underwent intravenous rt-PA treatment before EVT (bridging therapy) if IVT was indicative; overall 83% and 88% of subjects in these two groups had received IVT, respectively[23]. Different meta-analysis demonstrated that bridging therapy, as compared to EVT alone, led to better clinical outcomes, lower mortality at 90 days, and higher successful recanalization rates without significantly increasing the risk of hemorrhagic complications[23,24]. A multicenter registry study in Taiwan also revealed the use of intravenous rt-PA before EVT was a significant predictor for total recanalization with odds ratio (OR) of 2.53 (95% CI, 1.11-5.79)[25]. Therefore, current guidelines suggest that patients eligible for IVT should receive intravenous rt-PA even if EVT is being considered[7,8].

However, without direct comparison of efficacy and safety between bridging therapy and EVT alone in clinical trials, there is still uncertainty regarding the role of rt-PA before EVT in patients with ischemic stroke. Additional thrombolysis before EVT indeed may increase the chance of early reperfusion and dissolve residual distal thrombi after EVT[26]. On the other hand, the rate of successful recanalization via IVT for proximally located thrombi is limited, and IVT may cause fragmentation or distal migration of the target thrombus impeding EVT approach[27]. Theoretically, rt-PA may also increase the risk of cerebral hemorrhage and neurotoxicity[28] and sometimes the time taken to initiate IVT might delay the start of the EVT procedure. Therefore, to test the benefit and risk of IVT in addition to EVT for patients with large cerebral vessel occlusion is important.

Clinical Trials of bridging therapy

The Direct Intraarterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion (DIRECT MT) trial is the first study, which enrolled patients having AIS within 4.5 hours after stroke onset in China, comparing the outcome between EVT alone (n=327) and bridging therapy (n=329)[29]. The study showed the noninferior of EVT alone to bridging therapy regard to functional outcome with adjusted common OR for modified Rankin scale (mRS) at 3 months of 1.07 (95% CI, 0.81-1.40; p=0.04 for noninferiority). The risks of sICH (4.3% vs 6.1%) and mortality (17.7% vs 18.8%) were similar between EVT alone and bridging therapy groups.

In two other similar but smaller trials, the Direct Endovascular Thrombectomy vs Combined IVT and Endovascular Thrombectomy for Patients With Acute Large Vessel Occlusion in the Anterior Circulation (DEVT) trial conducted in China also showed the noninferiority of EVT alone (n=116) as compared to bridging therapy (n=118) in favorable outcome at post-stroke 90 days (54.3% vs 46.6%, p=0.003 for noninferiority)[30]. No significant differences were detected in sICH (6.1% vs 6.8%) and mortality (17.2% vs 17.8%) between groups. However, the Direct Mechanical Thrombectomy in Acute LVO Stroke (SKIP) trial conducted in Japan did not demonstrate the noninferiority of EVT alone (n=101) than bridging therapy (n=103) in favorable outcome at 90 days (59.4% vs 57.3%, p = 0.18 for noninferiority)[31]. The risk sICH (5.9% vs 7.7%) and mortality (7.9% vs 8.7%) were similar between groups.

Taken together, these 3 trials demonstrated that the treatment strategies of EVT alone and of bridging therapy yield numerically similar results for patients with AIS and having large vessel occlusion and EVT might be reasonable to consider for patients who present directly to EVT-capable centers with timely available of the EVT team[32]. Three other large clinical trials are still ongoing to reconfirm the results and to determine whether these

findings can generalize to non-Asian patients, including SWIFT-DIRECT trial (NCT03192332), MR CLEAN NO-IV trial (ISRCTN80619088) and DIRECT SAFE trial (NCT03494920).

Thrombolysis in Specific Patient Groups

Elderly

Updated meta-analysis demonstrated that IVT has a positive benefit-risk profile among AIS patients aged more than 80 years[33]. Intravenous rt-PA treatment, as compared to placebo control, was associated with a higher proportion of favorable outcome (19.1% vs 13.1%, p=0.011) and with similar 90-day mortality (29.5% vs 30.2%), although the risk of sICH was also higher in the IVT group (19% vs 2%, p=0.0002). For nonagenarians, a multinational registry study showed less post-stroke disability for those receiving IVT than control subjects without significant difference in sICH and in-hospital mortality rates between groups[34]. Therefore, octogenarians and nonagenarians are still able to get benefits from IVT upon AIS.

Minor stroke

The Potential of rtPA for Ischemic Strokes With Mild Symptoms (PRISMS) trial evaluated the efficacy and safety of IVT in patients with NIHSS scores of 0 to 5 whose deficits are not clearly disabling (preventing performing basic activities of daily living or returning to work)[35]. The study showed that IVT as compared to aspirin treatment did not increase the likelihood of favorable outcome at 90 days (78.2% vs 81.5%). Another study compared the therapeutic effects of IVT, aspirin, and dual antiplatelet agents in stroke patients with NIHSS of 0 to 3, which revealed no significant advantage of IVT over aspirin or dual antiplatelet therapy[36]. Therefore, IVT may not benefit patients with minor stroke, especially those with non-disable stroke.

Non-vitamin K antagonist oral anticoagulants

Recent meta-analysis demonstrated that prior intake of non-vitamin K antagonist oral anticoagulants (NOACs) appeared not to increase the risk of sICH in selected stroke patients treated with IVT[37]. However, since there is still no randomized trial to test the safety of IVT in NOAC users, current guidelines did not suggest to perform IVT directly in patients taking NOAC within 2 days[7,8]. Idarucizumab is a specific reversal agent of dabigatran, which is a direct thrombin inhibitor. Idarucizumab can rapidly, durably, and safely reversed the anticoagulant effect of dabigatran in emergency situations[38]. In stroke patients receiving idarucizumab to reversed the effect of dabigatran prior to IVT, the early post-thrombolysis outcomes including NIHSS change, sICH, and mortality were similar compared with patients not exposed to dabigatran/idarucizumab[39]. Ten Taiwanese dabigatran-treated stroke patients who received idarucizumab then IVT showed significant functional improvement after IVT, except one with large infarct and fatal sICH.[40], which reconfirmed the feasibility of the treatment strategy in dabigatran users (Figure 2).

Cerebral microbleeds

Cerebral microbleeds (CMBs) can be detected using susceptibility weighted imaging or T2* of brain MRI sequences and CMBs are common in patients receiving IVT (15% to 27%)[41]. A higher risk for sICH after IVT was detected in patients with high CMB burden (>10 CMBs) when compared with patients with 0 to 10 CMBs (RR, 12.10; 95% CI, 4.36-33.57) on pretreatment MRI[41]. The presence of CMBs, especially with high burden (>5 CMBs) and lobar location, were significantly associated with less favorable 3-month outcomes (OR, 0.57; 95% CI, 0.33-0.97) after IVT or EVT[42]. The analysis for the net treatment effect of IVT in patients with >10 CMBs were in favor of withholding IVT in older patients with more severe strokes and longer treatment delays[43]. However, without available randomized control trials to investigate the outcome for patients with high burden of CMBs receiving IVT, it is unclear whether these negative effects of CMBs fully negate the benefit of IVT.

Epilepsy

Seizure at stroke onset occurred in 1.5% of patients receiving IVT[44]. Because patients with seizure at stroke onset were excluded from the major trials[2], the evidence for the use of IVT in such patients is limited. In patients receiving IVT, those with seizure at stroke onset had higher stroke severity and more often prior stroke and preexisting dependence[44]. After controlling for confounders, seizure at stroke onset was not a predictor for sICH, mortality or functional outcome. It support the

current guideline that IVT is reasonable for patients with seizure at stroke onset if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon[7].

Other Thrombolytic Agents

Early thrombolytic agents

In addition to rt-PA, various thrombolytic agents have been studied or are undergoing investigation in AIS. Treatment with streptokinase in acute stroke resulted in an increase in mortality than placebo control (34.0% vs 18.2%, p=0.002), mainly due to increased risk of fatal sICH[45]. Desmoteplase, isolated then reproduced from the saliva of the vampire bat, had higher fibrin selectivity than rt-PA (190-fold). Unfortunately, a large clinical trial failed to show the functional improvement when desmoteplase was given within 3-9 hours post-stroke in patients with large vessel occlusion[46].

Tenecteplase

As compared to rt-PA, TNK, a genetically engineered mutant rt-PA, was developed with higher fibrin specificity (14-fold), greater resistance to inactivation by plasminogen activator inhibitor-1 (80-fold), and longer free plasma half-life (6-fold), allowing single intravenous bolus administration[47]. In 2005, a pilot dose-escalation study of TNK was conducted, showing the safety of TNK at the doses of 0.1 to 0.4 mg/kg in AIS[48]. In the following randomized clinical trials, for patients with large vessel occlusion existing penumbra (n=75) noted by CT angiography and CTP in the Australian TNK trial, TNK (0.1 or 0.25 mg/kg) was associated with better reperfusion (79.3% vs 55.4%, p=0.004) and more improvement in NIHSS at 24 hours (8 vs 3, p<0.001) than rt-PA within 6 hours post-stroke[49]. Further two trials using only CT for patient selection, including the Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST) (n=104) and Norwegian Tenecteplase Stroke Trial (NOR-TEST) (n=1100) trials, both reported no difference between TNK (0.25 or 0.4 mg/kg) and rt-PA treatment with respect to either safety or efficacy within 4.5 hours post-stroke[50,51]. The Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial enrolled patients with AIS who had large vessel occlusion and were eligible to undergo EVT to receive TNK (0.25 mg mg/kg) or rt-PA (n=101 in both groups) within 4.5 hours after symptom onset[52]. The study showed that TNK before thrombectomy was associated with a higher incidence of reperfusion (22% vs 10%, p=0.03) and better functional outcome (mean mRS, 2 vs 3, p=0.04) than rt-PA. The following EXTEND-IA TNK part 2 trial further confirmed that a dose of 0.40 mg/kg, compared with 0.25 mg/kg, of TNK did not significantly improve cerebral reperfusion prior to EVT[53]. Taken together, stroke patients with large vessel occlusion receiving TNK have significantly better recanalization and clinical outcomes compared with those receiving rt-PA[54].

Many clinical trials regarding TNK thrombolysis in stroke are still ongoing. The ATTEST-2 (NCT02814409) and NOR-TEST 2 (NCT03854500) trials aim to recruit patients on CT and clinical criteria alone and compares TNK (0.25 mg/kg or 0.4 mg/kg) with rt-PA. The TASTE trial (ACTRN12613000243718) enrolls stroke patients who fulfill target mismatch criteria on CTP and compares TNK (0.25 mg/kg) with rt-PA without further EVT. The TWIST trial (NCT03181360) aims to enroll patients with wake-up stroke and compares TNK (0.25 mg/kg) versus non-thrombolytic standard of care without perfusion imaging criteria. The TEMPO-2 trial (NCT02398656) randomizes minor non-disabling AIS patients (NIHSS 0-5) with intracranial arterial occlusion to TNK (0.25 mg/kg) versus nonthrombolytic standard of care. The TIMELESS trial (NCT03785678) compares TNK (0.25 mg/kg) with placebo in AIS patients having penumbra within 4.5-24 hours after onset additional to standard of care.

CONCLUSION

Significant progress regarding IVT in AIS has been achieved in the past few years. With assistance from advanced cerebral imaging, the time window of IVT is extended to be post-stroke 9 hours and wake-up stroke is not totally contraindicative for IVT. For patients with large vessel occlusion, EVT alone is likely non-inferior to bridging therapy. However, the principle to select either or both reperfusion therapy in different situations still requires further investigation. To improve the efficacy and safety, the use of IVT for various specific groups of patients needs to be optimized. Recent clinical trials of a new thrombolytic agent TNK, have shown promising

results and the drug may have potential to replace rt-PA in the future. Early and appropriate application of IVT and/or EVT in correctly selected stroke patients with standardized post-treatment management will substantially reduce the major global burden of disability related to stroke.

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